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ORIGINAL ARTICLE

# A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group

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**A widely accepted definition of resistance or intolerance to hydroxyurea (HU) in patients with essential thrombocythemia (ET) is lacking. An international working group (WG) was convened to develop a consensus formulation of clinically significant criteria for defining resistance/intolerance to HU in ET. To this aim, an analytic hierarchy process (AHP), a multiple-attribute decision-making technique, was used. The steps consisted of selecting the candidate criteria for defining resistance/intolerance; identifying the motivations that could influence the preference of the WG for any individual criterion; comparing the candidate criteria in a pair-wise manner; and grading them according their ability to fulfill the motivations. Every step in the model was derived by questionnaires or group discussion. The WG proposed that the definition of resistance/intolerance should require the fulfillment of at least one of the following criteria: platelet count greater than 600 000/μl after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight over 80 kg); platelet count greater than 400 000/μl and WBC less than 2500/μl or Hb less than 10 g/dl at any dose of HU; presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU; HU-related fever.**
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## Introduction

Hydroxyurea (hydroxycarbamide, HU) is a non-alchilating antineoplastic agent widely used for the treatment of myeloproliferative diseases, which interrupts the normal mechanism of reduction of ribonucleotides and deoxyribonucleotides through the inactivation of ribonucleotide reductase, limiting DNA biosynthesis.[1] HU may carry more or less severe side effects: macrocytosis, neutropenia, leg and oral ulcers, cutaneous rash, skin dryness, nail pigmentation, cystitis, fever and gastrointestinal symptoms.[2,3] Moreover, a slight increase in skin cancer has been reported in patients on HU.[4] Finally, the possible relationship between long-term therapy with HU and leukemic transformation is still a matter of debate.[3]

HU is regarded as the first-choice platelet-lowering therapy in most of patients with essential thrombocythemia (ET) according to suggestions from experts in the field,[5,6] from evidence-based guidelines,[7] and from the results of the MRC-PT1 study.[8] However, up to 10% of the patients do not attain the desired reduction of platelet number with the recommended dose of the drug, thus exhibiting clinical resistance, whereas some will develop unacceptable side effects, demonstrating clinical intolerance.[3,7–9] Despite these facts, there is neither widely accepted definition of resistance nor of intolerance to HU, and different authors have proposed different definitions that were used either as a stopping rule in clinical trials or as management recommendation in clinical practice.[3,8–10]

The absence of accepted criteria and the marked heterogeneity in the definitions of resistance/intolerance to HU in ET, largely prevent any comparisons of the published reports. Thus, a meaningful figure of the rate of resistance/intolerance to HU in ET is lacking. A strict definition of resistance/intolerance to HU is desirable for clinical studies aiming at assessing the efficacy of platelet-lowering treatment of ET, particularly of second-line therapies, like interferon and anagrelide. Such a definition is also valuable for the clinical management of the patients, particularly after the approval of anagrelide in European countries from the agency for drug approval (EMEA) which allowed the drug to be used as second-line therapy in 'at-risk ET patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy'.[11]

An international working group (WG) was formed with the intention to produce, by a consensus process, a proposal for a definition of resistance/intolerance to HU in patients receiving the drug for ET as an initiative of the Chronic Myeloproliferative Disorders Working Party of the European Leukemia Net, a network of excellence project funded by the European Community. The WG was aware that providing criteria for resistance/intolerance to HU required the selection of measurements that were multifactorial in nature and whose metrics were highly variable and difficult to define accurately. In an attempt to consider all the factors that may affect the definition of resistance/intolerance to HU, an analytic hierarchy process (AHP), a multiple-criteria decision-making technique, was

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employed.[12] Factors contributing to the choice of AHP include its ability to simplify a complex problem in a concise easily understood fashion and procedural simplicity. The final purpose of the project was to identify rigorous, consistent and feasible criteria applicable to future clinical trials and also to routine practice.

## Methods

The definition of resistance/intolerance to HU in patients with ET was developed by a multistep process. A WG was constituted in December 2005, composed of 15 experts in chronic myeloproliferative disorders, and was chaired by a clinician with expertise in clinical epidemiology (GB).

### *Framing the decision model*

During the initial meeting, the WG agreed on the goal of the project: to develop criteria for defining clinically significant resistance and intolerance to HU in patients with ET treated with this drug as platelet-lowering therapy. The WG agreed that resistance and intolerance to HU are inter-related constructs, so the goal was to produce a unified definition for them.

To create a decision model according to the AHP analysis, and given the goal of the project, the motivations to be used for evaluating how well the criteria produced would meet the goal were discussed in detail during the initial meeting. It was agreed that three motivations could influence the decision of preferring one criterion to another for resistance/intolerance to HU, namely: (a) avoid continuation of the drug when it has proven to be ineffective in 'high-risk' disease; (b) avoid immediate and long-term side effects of unnecessary continuation of the drug; (c) avoid premature discontinuation of the drug whose efficacy could be retarded. Figure 1 shows the way the decision for selecting from the possible criteria could be framed as an AHP model.

### *Selecting the criteria*

We defined 'criterion' to be used in the definition of resistance/intolerance to HU, any condition during the HU therapy that, when occurring, can have a significant impact on the management of patients with ET, and that could lead to the discontinuation of the drug. We first aimed at selecting the criteria in their conceptual terms, worded without any numerical or quantitative attributes. To achieve this, a questionnaire was mailed to each member of the WG asking them to propose candidate conceptual criteria that were further refined in a Delphi process[13] with a second questionnaire that asked to rank the top choices among candidate criteria. All the questionnaires were returned and the candidate conceptual criteria were ranked according to their priority votes, with the criteria that ranked highest and that received at least 80% consensus to be included in the list, forming the core set of conceptual criteria.

We then aimed at selecting the criteria in their operational terms populating them with quantitative or numerical attributes. To assess and select operational criteria, a third questionnaire requested that the WG proposed candidate operational criteria for each conceptual criterion. Subsequently, the WG ranked these operational criteria and the highest-ranking ones (>80% consensus) formed the candidate operational criteria.

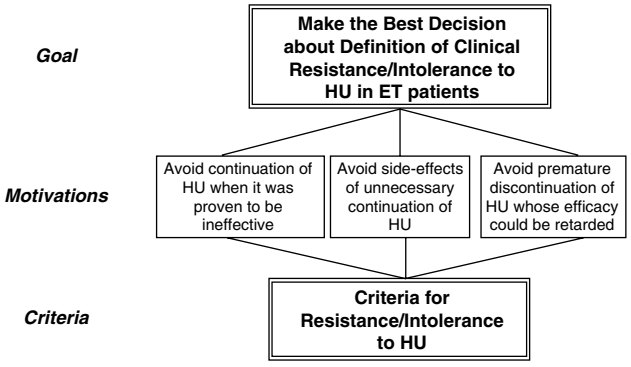


**Figure 1** AHP model regarding the selection of criteria for resistance/intolerance to HU in patients with essential ET. At the top is the goal of the decision; at the bottom are the criteria to be decided; in the middle are three motivations used for evaluating how well the options meet the goal.

### *Pairwise comparison of operational criteria*

The next step was to determine the importance of each candidate operational criterion by pair wise comparison. Using a bottom-up approach, the criteria were subjected to comparison according to their ability to fulfill one of the three decision motivations preliminarily selected for the decision according to the preferences of the members of the WG. This part of the process was exploited in a consensus meeting using the nominal group technique.[14] The comparisons were made between two criteria at a time and each member of the WG was asked to choose for that particular comparison which of the two he/she considered more important for making the best decision. The option achieving at least 80% consensus was then successively ranked pair wise with the next in a progressive manner until every pair of criteria has been evaluated. This process clarified the expert's judgments regarding which considerations are pertinent and their relative importance, facilitating an open discussion during the consensus process.

## Results

### *The conceptual criteria*

The WP listed eight conceptual criteria to be included as candidates for the definition of resistance/intolerance to HU. The four with the highest preference rate (>80% consensus) were: (a) not achieving the desired reduction of platelet count after a critical time period at the maximum tolerated dose of the drug; (b) not achieving the desired reduction of platelet count but achieving a drug-dependent critical reduction of white blood cells (WBC); (c) not achieving the desired reduction of platelet count but achieving a drug-dependent critical reduction of hemoglobin; (d) appearance of unacceptable clinical side effects.

### *The candidate operational criteria*

The WG listed 47 operational criteria to be included as candidate criteria for the definition of resistance/intolerance to HU. Twelve of them with the highest preference rate (>80% of consensus) are listed in Table 1. The first three criteria operatively translated the motivations: 'avoid continuation of the drug when it has proven to be ineffective in high-risk disease', and 'avoid premature discontinuation of the drug whose efficacy could be retarded', and represented the different views among the experts about the number of platelet and time

**Table 1** Candidate operational criteria for the definition of resistance/intolerance to HU in ET patients

| |
|---|
| Platelet count > 600 000/$\mu$l after 3 months of at least 2.5 g/day of HU |
| Platelet count > 600 000/$\mu$l after 3 months of at least 2 g/day of HU |
| Platelet count > 1 000 000/$\mu$l after 2 months of at least 2.5 g/day of HU |
| WBC < 3000/$\mu$l and platelet count > 600 000/$\mu$l after 3 months of at least 2 g/day of HU |
| WBC < 2000/$\mu$l and platelet count > 600 000/$\mu$l after 3 months of at least 2 g/day of HU |
| Hb < 8 g/dl and a platelet count > 600 000/$\mu$l after 3 months of at least 2 g/day of HU |
| Hb < 10 g/dl and a platelet count > 600 000/$\mu$l after 3 months of at least 2 g/day of HU |
| Hb < 10 g/dl and a platelet count > 500 000/$\mu$l after 3 months of at least 2 g/day of HU |
| Mucocutaneous manifestations unacceptable to the patient at any dose of HU |
| Oral or leg ulcers at any dose of HU |
| HU-related fever on treatment with HU at any dose |
| Symptomatic muco-cutaneous alterations at any dose of HU |

Abbreviations: ET, essential thrombocythemia; HU, hydroxyurea.

**Table 2** Definition of resistance/intolerance to HU in patients with ET

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| Platelet count < 600 000/$\mu$l after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight > 80 kg) |
| Platelet count < 400 000/$\mu$l and WBC less than 2500/$\mu$l at any dose of HU |
| Platelet count < 400 000/$\mu$l and Hb less than10 g/dl at any dose of HU |
| Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU |
| HU-related fever |

Abbreviations: ET, essential thrombocythemia; HU, hydroxyurea; WBC, white blood cells.

for defining ineffectiveness of the therapy. The other criteria operatively translated the motivation 'avoid immediate and long-term side effects of unnecessary continuation of the drug'.

### *Pairwise selection of the criteria*

Using the pairwise comparisons, the 15 members of the WG proposed that the definition of resistance/intolerance should require the fulfillment of at least one of the criteria reported in Table 2. The motivations for the decision varied among the members of the WG, but most preferred to adopt a precautionary principle that facilitated the conservative attitude of avoiding side effect, both immediate and long term, of an unnecessary use of the drug early after documentation of ineffectiveness. This even though agreement was declared that the long-term side effects of HU, like carcinogenesis, are not clearly demonstrated.

## Discussion

We report the results of a consensus process in achieving a definition of resistance/intolerance to HU in patients with ET. In the absence of scientific evidence of the risk of continuing therapy after the documentation of a suboptimal response, the WG was aware that searching for a definition of resistance/intolerance to HU raised a complex decision issue, with the pending drawbacks of the subjective and arbitrary nature of the resulting criteria. To focus the problem, the panel of experts used group techniques with the assumption that such acknowledged experts have an implicit and comprehensive mastery of scientific and practical information that would yield the most appropriate definition. The value of such a consensus approach to the definition of operational criteria in medicine has been exploited in a high number of similar processes reported in the literature.[15,16] In this work, group decision approach was based on AHP multiple criteria decision-making process for overcoming many of the cognitive and practical problems of decision problems that need to select measurements that are multifactorial in nature, such as the problem at hand. The AHP decision model was adopted to help reducing a complex problem into small, easily managed parts, ensuring that all important considerations are taken in mind, and integrating multiple viewpoints into the decision-making process in an explicit and unbiased manner. The clinical effectiveness of decision-making programs based on multicriteria methods has been determined, and data suggest that they can be implemented with beneficial results.[17–21]

The results of this project suggest that resistance/intolerance to HU can be defined with five critical events as specified in Table 2. This definition is constructed of criteria widely used in different definitions of the so-called resistance, ineffectiveness, unresponsiveness or intolerance to HU previously reported in the literature,[3,8–10] but not in this precise combination. The performing characteristics of the resulting definition should be interpreted acknowledging the uncertainty inherent both to the consensus process and to the panelists' preferences and attitudes. The former depends on the size of the expert panel and the effectiveness of the decision model; the latter reflects the absence of scientific evidence upon which to base the definition.

The treatment of ET is problematic, and few evidence-based directives can be given. The WG deliberately did not address treatment guidelines but focused instead upon the important issue of when to consider switching from therapy with HU to that with other molecules. This will guide clinicians in when to use drugs such as anagrelide that are licensed by the EMEA only after resistance or intolerance to first-line therapy has been documented. Moreover, these results may be adopted in protocols of clinical trials in ET as stopping rule of the first-line therapy with HU or inclusion criteria of second-line therapy after HU.

In conclusion, the WG proposes the use of the presented definition of resistance/intolerance to HU in ET patients, which was developed using a strict AHP-based consensus process and offers a definition to be adopted for clinical use, especially for scientific trials.

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